Editorial

Antifungal use in intensive care units: another uncertainty that highlights the need for precision medicine

Rima Moghnieh[1], Zeina A. Kanafani[2], Souha S. Kanj[2]

[1]Makassed General Hospital, Beirut, Lebanon; [2]American University of Beirut Medical Center, Beirut, Lebanon

Correspondence to: Souha S. Kanj, MD, FACP, FIDSA, FRCP. Professor of Medicine; Head, Division of Infectious Diseases; Chairperson, Infection Control Program, American University of Beirut Medical Center, PO Box 11-0236, Riad El Solh, 1107 2020, Beirut, Lebanon. Email: sk11@aub.edu.lb.

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Epidemiologic data have shown an increasing prevalence of candidemia in non-immunocompromised critically ill patients (1). *Candida* is the fourth most common organism causing bloodstream infections in hospitals, accounting for 10% of all bloodstream infections with an attributable mortality ranging from 42% to 63% (2-6) leading to increased intensive care unit (ICU) and hospital stay (7,8). In some studies one half to two-thirds of all episodes of candidemia are acquired in ICUs (2-6).

As early initiation of antifungal therapy has been associated with decreased mortality in patients with candidemia (9), there has been a trend of using antifungals empirically in high-risk ICU patients with signs of sepsis, in the absence of microbiological evidence of infection. Timsit and colleagues (10) conducted a multicenter double blind placebo controlled trial (EMPIRICUS) in 19 French ICUs aiming at determining, as a primary end point, whether empiric micafungin reduces fungal-free survival at day 28 after enrollment. The investigators randomized 260 critically ill patients with ICU-acquired sepsis of unknown origin. These patients were under mechanical ventilation, with at least one additional organ dysfunction, with evidence of *Candida* colonization other than the gastrointestinal tract, exposed to broad-spectrum antibiotics, and with at least one arterial or central venous catheter. On day 28, there was no statistical significance in the primary outcome between the two groups, where 68% of patients in the micafungin arm *vs.* 60.2% in the placebo arm were alive and free of invasive fungal infection (IFI). The use of empirical micafungin did, however, decrease the rate of new IFI in 4/128 patients (3%) in the micafungin arm *vs.* placebo arm (15/123 patients [12%]) (P=0.008). In addition, the number of organ failure-free days and the rate of VAP were not significantly different between the 2 groups. Likewise, patients with a (1-3) beta D-glucan (BDG) level >80 pg/mL or sequential organ failure assessment (SOFA) score >8 did not show any statistical significant difference between the two arms in terms of IFI-free survival at 28 days of enrollment in the modified intent-to-treat population and in predefined subgroups. Yet, there was a trend towards clinical significance favoring the use of micafungin in patients with BDG levels >80 pg/mL, BDG levels >250 pg/mL, *Candida* scores at ≥3, and colonization index ≥50%.

The EMPIRICUS trial was preceded by conflicting evidence from the literature regarding the usefulness of systemic antifungal therapy (SAT) in ICU patients. In a cross-sectional cohort study including 2,047 patients from 169 French and Belgian ICUs, Azoulay and colleagues (11) found that SAT was used in 7.5% of the enrolled patients. However, 67% of patients given SAT had no documented IFI, and the 28-day mortality did not differ between those who received and those who did not receive SAT. Another recently published multicenter prospective observational study by the same group of investigators

involving 1,491 patients from 5 French ICUs similarly failed to show outcome benefits for empirical SAT in reducing mortality or invasive candidiasis in critically ill and mechanically ventilated patients, using a nonbiased method for longitudinal data analysis (12). Both studies concluded that a trial to refine indications for SAT in the absence of documented IFI based on surrogate markers of invasive candidiasis is warranted. Finally, a recent Cochrane systematic review assessed the effects of antifungal therapy in critically ill patients in terms of all-cause mortality and incidence of proven IFI as primary outcomes (13). This review involved 2,761 patients from 22 RCTs. There was moderate grade evidence that untargeted antifungal treatment did not significantly reduce total all-cause mortality [relative risk (RR) 0.93, 95% CI: 0.79–1.09, P=0.36]. However, there was a low-grade evidence that these strategies significantly reduce by about 45% the incidence of proven IFI (RR 0.57, 95% CI: 0.39–0.83, P=0.0001).

Three major randomized controlled trials (RCTs) before the EMPIRICUS trial evaluated the usefulness of empiric antifungal therapy in ICU. The first trial, by Schuster and colleagues (14), compared high-dose fluconazole with placebo in 270 adult patients with fever despite administration of broad-spectrum antibiotics in 26 US ICUs. The second trial MSG-01, by Ostrosky-Zeichner and colleagues (15) tested the use of caspofungin versus placebo in 222 ICU patients whose recruitment was based on nosocomial sepsis. Both trials showed no reduction of IFI-free survival at day 30 after enrollment in the SAT group, yet unlike the EMPIRICUS trial, SAT did not even have an effect on the rate of new episodes of invasive candidiasis. The third trial, MSG-04 (ClinicalTrials.gov identifier: NCT01045798), also comparing empirical therapy using caspofungin versus placebo for invasive candidiasis in high-risk critically ill patients, was prematurely interrupted in 2015 due to insufficient number of enrolled patients.

The EMPIRICUS trial represents a continuum of ongoing research regarding antifungal therapy in ICUs. Although it is titled as "empirical treatment", it rather represents a preemptive approach, taking into consideration both host factors, clinical criteria and mycological factors like the *Candida* colonization. Compared to studies that assessed the colonization index as a sole parameter for initiation of SAT (16), the EMPIRICUS trial included more specific clinical inclusion criteria, such as ongoing sepsis, multiple organ dysfunction, and length of ICU stay. Ferreira and colleagues (16) demonstrated that the use of the colonization index alone is clearly inappropriate to initiate pre-emptive antifungal therapy, since 26% of patients had a colonization index >0.5, and this has led to an overuse of antifungals in a surgical ICU over an 8-year period. Furthermore, the colonization-based pre-emptive antifungal prescription generated a significant change in acquired colonization, especially with the non-albicans species, without having any impact on incidence of candidemia or on *Candida*-related mortality (16).

Although the inclusion criteria in the EMPIRICUS trial were designed to identify the patients at considerable risk for IFI, only 5% of enrolled patients had an abdominal surgery, and 6% had necrotizing pancreatitis, these being very strong risk factors predisposing to IFI. The authors recognize this as a limitation to their study. Obviously, designing a study that includes preferentially ICU patients following abdominal surgery would require a larger overall sample size. In fact, the sample size calculation in the EMPIRICUS trial is quite intricate and was based on several assumptions. The investigators proposed a difference of 18% in the primary outcome as their target margin. This is significantly larger than the more commonly used 10% margin of difference in non-inferiority trials. The calculated difference in primary outcome at the end of the trial was 7.8% in favor of micafungin. At a target difference of 10%, and with a larger sample size, there is a possibility that a significant difference in primary outcome would have been achieved.

As far as the secondary endpoints are concerned, the authors found a significant reduction in the total number of IFI events (3% with micafungin and 12% with placebo; P=0.008). The importance of this finding should not be discounted. Although it did not translate into statistically significant survival advantage, decreasing the incidence of IFI has a merit in itself. Interventions in critical care are not always guided by mortality rates. Other points of interest that have been used in various studies include length of ICU and hospital stay, hospital costs, total antifungal use, total antibiotic use, duration of mechanical ventilation, among others. Another valid question raised by the investigators is whether the 100 mg dose of micafungin, which resulted in suboptimal levels, is the right dose in the critically ill patients suggesting that higher doses may be necessary in such patient populations.

Although the EMPIRICUS trial is well designed and statistically well powered, it does not give us a final verdict about the use of antifungals in ICUs. However, it calls for additional future research in this field. Perhaps in particular,

addressing the use of SAT versus placebo in specific subgroups of critically ill surgical patients such as those with intra-abdominal surgeries or necrotizing pancreatitis with ongoing-sepsis, and a BDG level >250 pg/mL (BDG being more accurate than both the *Candida* score and the colonization index for early prediction of invasive *Candida* infection in patients at risk for *Candida* sepsis, with 250 pg/mL identified as the best cutoff value (17). If such RCTs show evidence of benefit in such subgroups, SAT would be recommended preemptively to specific ICU subpopulations.

This is a yet another example where precision medicine might be applied. It highlights the need of having detailed algorithms in guiding antifungal use in ICU, taking into consideration not only general risk factors for IFI but also specific emphasis on particular hosts, clinical and mycological factors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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